REMARKS

Claims 32-33, 47-48 and 74 have been amended. Claim 77 has been added. Claims 34-35, 39, 72 and 73 are presently canceled. Claims 1-31, 38, 40, 58-71 and 76 were previously canceled.

Applicants note that claims 72-76 were previously presented in the Amendment mailed August 22, 2003, and acknowledged by the Office in the Office Action mailed December 4, 2003 and June 2, 2004. Claim 76 was subsequently canceled in the Amendment mailed October 4, 2004. However, claims 73-75 are not listed in the list of pending claims in this Office Action. Applicants assume this was an inadvertent error, and that claims 32-33, 36-37, 41-57, 74-75 and 77 are presently pending. Support for the amendments can be found throughout the specification and is discussed in more detail below.

Applicants and Applicants' representatives gratefully acknowledge the careful consideration of the application and helpful suggestions made by the Examiner in the telephone interview held on April 4, 2005. Amendments to the claims have been made pursuant to the telephone interview with Examiner Pak, whereby Applicants discussed amending the claims to Rpn11 and AMSH polypeptides in order to put the claims in condition for allowance. Applicants submit that a new search is not necessary, and that all amendments are supported by the previously pending claims.

I. Amendments to the claims

Claim 32 has been amended to provide a complete recitation of the JAMM domain as comprising Jab1/Mpn/Mov34 metalloenzyme. Claim 32 has also been amended to recite that the polypeptide having a JAMM domain and isopeptidase activity is "Rpn11, or Rpn11 complex, or (SH3 domain of STAM) AMSH."

Claims 34-35 and 39 have been canceled because their subject matter is related to COP9 signalsome (CSN), and CSN is not the claimed subject matter of the instant application.

Claims 72 and 73 have been canceled because their subject matter has been incorporated into amended claim 32.

Claim 74 has been amended to correct its dependency from that of 72, a cancelled claim, to that of claim 32.

The above amendments do not add new subject matter and are fully supported throughout the specification as will be discussed in more detail below.

II. Rejection Under 35 U.S.C. §112 first paragraph (written description)

a. Claims 32-37, 39, 41-57 and 72-73 are rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

According to the Office Action, the claims are allegedly drawn to a method of using a polypeptide having isopeptidase activity comprising the JAMM domain of SEQ ID NOs: 1 and 2, and that the claims are therefore drawn to polypeptides having "any" structure (page 3 of Office Action).

Claims 34-35, 39, 72 and 73 have been cancelled, thus making the rejection with regards these claims moot.

Claim 32 has been amended to incorporate the subject matter of dependent claims 72 and 73. Claim 32 has also been amended to include AMSH. Hence, amended claim 32 recites a method of identifying an agent that affects isopeptidase activity of a polypeptide, "wherein the polypeptide is Rpn11, or RPN11 complex, or (SH3 domain of STAM) AMSH."

The written description requirement is met when the subject matter is described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Possession may be shown by: i) describing an actual reduction to practice of the claimed invention; or ii) a clear depiction of the invention in detailed drawings ... which permit a person skilled in the art to clearly recognize that applicant had possession of the claimed invention. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000).

The claimed subject matter is reduced to practice in Examples 1 and 3. Example 1 shows that the 26S proteasome containing the Rpn11 complex, or Rnp11 protein, has isopeptidase activity; and this activity is conferred by the JAMM domain found in the Rpn11 proteins. To establish that the JAMM domain in fact confers the isopeptidase activity, the conserved histidine residues of the Rpn11 JAMM domain were mutated to alanine (*rpnAxA* mutant). The wild-type (or non-mutated *rpn11*) and the *rpnAxA* mutant were then co-transfected into Rpn11-deficient temperature sensitive cells (*mpr-1-1* temperature sensitive allele of *Rpn11*), and results show that wild type *rpn11* restored isopeptidase (or deubiquinating) function to the temperature sensitive *mpr1-1* cells (see paragraph [0069]). Therefore, Rpn11, a polypeptide having isopeptidase activity and containing the JAMM domain, confers isopeptidase activity and is required for rapid turnover of proteins by the ubiquitin-proteasome pathway *in vivo* (paragraph [0071]; and FIG. 1). Example 1, also shows by an immunoblot assays using antibodies directed against Sic1, that Rpn11AxA mutant 26S proteasomes in the presence, or even in the absence, of epoxomicin are unable to deubiquinate (or degrade) Sic1 (paragraph [0075]). Hence, Rpn11 is necessary for the

deubiquination of ubiquinated proteins, and mutating the conserved histidines of the Rpn11 JAMM domain to alanine shows that the domain confers the isopeptidase activity.

Claim 32 also recites an AMSH polypeptide having isopeptidase activity and a JAMM domain. Example 3 shows that the conserved histidines and aspartate residues of the AMSH, AMSH1 and AMSH2 JAMM domains confer metalloprotease, or isopeptidase activity; and that inhibitors of isopeptidase activity inhibit the ability of AMSH proteins to deubiquinate (or degrade) ubiquinated proteins (see paragraphs [0087] to [0090]; and FIG. 2).

Therefore, the claimed subject matter is sufficiently described in the specification, and reasonably conveys to one of ordinary skill in the art that the Applicants, at the time the application was filed, had possession of the of the claimed invention.

Accordingly, withdrawal of the rejection of claims 32-37, 39- 41-57 and 72-73 under 35 U.S.C. §112, first paragraph is respectfully requested.

III. Rejection Under 35 U.S.C. §112 first paragraph (enabling)

Claims 37-46 and 48-66 are rejected under 35 U.S.C. §112, first paragraph as allegedly not enabling the claimed method. Applicants respectfully traverse this rejection.

According to the Office Action, the claims are allegedly drawn to a method of using a polypeptide having isopeptidase activity comprising the JAMM domain of SEQ ID NOs: 1 and 2, and that the claims are therefore drawn to polypeptides having "any" structure (page 3 of Office Action).

Applicants note that claims 58-71 were previously canceled in the Amendment mailed August 22, 2003; and that claims 38 and 40 were canceled in the Amendment mailed October 4, 2004. Also, claim 39 has been cancelled, thus making the rejection with regards to claim 39 moot. However, to be fully responsive, Applicants submit the following arguments as they relate generally to the claimed subject matter of pending claims 32-33, 36-37, 41-57, 74-75 and 77, and therefore encompassing the subject matter of rejected claims 37-46 and 48-66.

According to the Office Action, Applicants, after application of the eight factors in *In re Wands*, do not enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). Applicants respectfully traverse this rejection, as discussed in detail below, and submit that all factors of *In re Wands* have been satisfied and no undue experimentation is necessary.

The 8 factors of *In re Wands*: (1) quantity of experimentation; (2) amount of direction or guidance; (3) presence or absence of working examples; (4) nature of the invention; (5) state of the prior art; (6) the relative skill of those in the art; (7) predictability or unpredictability in the art; and (8) the breadth of the claims. Discussion of the factors is as follows:

(1) The quantity of experimentation necessary is minimal because Examples 1 and 3, fully enable one skilled in the art to make and use the invention. First, because the Rpn11 and AMSH contain JAMM domains as described in SEQ ID NO:1, or HXHXXXXXXXXXXD

(see FIG. 3; claim 32; and Example 1). Secondly, because the *in vivo* and *in vitro* results as described in the specification conclusively demonstrate that the JAMM domain of these proteins are essential for deubiquintination of the ubiquinated target protein.

(2) There is sufficient guidance and direction provided throughout the specification, in particular, Examples 1 and 3, such that one of ordinary skill in the art can duplicate and achieve the end result.

(3) Examples 1 and 3 are working examples, which show that the JAMM domain is necessary for deubiquintination of the target polypeptide, or modified target protein or ubiquinated target protein. Also, that in the presence of epoxomicin, a peptidase inhibitor, Rpn11 and AMSH proteins are unable to deubiquinate ubiquinated proteins. Moreover, Example 1 shows that mutating the conserved histidines in the JAMM domain (i.e. HXHXXXXXXXXXXD) to alanine (i.e. AXAXXXXXXXXXXD) is lethal. That is, cells harboring the *Rpn11AxA* mutation did not have rapid turn over of proteins by the ubiquitin-proteasome pathway (see paragraph [0071]). These examples demonstrate the function of Rpn11 and AMSH.

(4) the nature of the invention is to provide methods for screening polypeptides having isopeptidase activity and a conserved JAMM domain, including Rpn11 and AMSH polypeptides.

(5) The function of the 26S proteasome and its role in substrate degradation (deubiquination) was unknown prior to the filing of the instant application. That is, the filing of the instant application was the first to report that polypeptides such as Rpn11 and AMSH, having isopeptidase activities and JAMM domains, are involved in deubiquintination of ubiquinated proteins.

(6) The relative skill of those in the art is high, but no higher than for other areas of molecular biology and biochemistry where identification and characterization of conserved sequences or motifs are tested *in vivo* and *in vitro* and the same is performed for various mutants thereof.

(7) Once a polypeptide having a JAMM domain and an isopeptidase activity is identified, the predictability of the activity of that polypeptide and its function in

deubiquinating proteins is substantially as described by the instant application. Support for this is shown in Examples 1 and 3 and a recent publication by McCullogh et al., describing the isopeptidase activity of AMSH proteins in the endosome (see Exhibit A, McCullogh et al., "AMSH is an endosome-association ubiquitin isopeptidase," *J. Cell Bio.*, 166(4)487-492 (2004)).

(8) Claim 32 has been amended, hence the breadth of the claim 32 and its dependent claims are to a species (e.g. Rpn11, or Rpn11 complex, or AMSH) and thus fully supported and enabled by the specification as discussed above (see Examples 1 and 3 and FIGs. 1-4).

Therefore, application of the eight *In re Wands* factors show that the claimed subject is enabling and no undue experimentation is required.

Accordingly, withdrawal of the rejection of claims 37-46 and 48-66 are under 35 U.S.C. §112, first paragraph is respectfully requested.

III. Conclusion

Applicants submit that the pending claims are in condition for allowance. Reexamination, reconsideration, withdrawal of the rejections, and early indication of allowance are requested respectfully. If any questions remain, the Examiner is urged to contact the undersigned below.

No fee is believed due in connection with this Amendment. If any additional fees are due, the Commissioner is hereby authorized to charge any fees that may be required by this paper to Deposit Account No. 07-1896. A duplicate copy of this Transmittal Sheet is attached.

Respectfully submitted,

Date: April 7, 2005

Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER RUDNICK GRAY CARY US LLP
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133
USPTO CUSTOMER NO. 28213